CHD1 Contributes to Prostate Cancer Development and Progression Through Cell-Intrinsic and -Extrinsic Mechanism

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Background: Prostate cancer (PCa) invariably becomes refractory to androgen deprivation therapy (ADT), resulting in the development of metastatic castration resistant prostate cancer (mCRPC) with high morbidity and mortality. A majority of localized and metastatic prostate cancer shows loss of PTEN; therefore, identification of specific therapeutic targets and effective combinations for PCa harboring deficiencies of PTEN holds hope for patients with advanced PCa. mCRPC shows overwhelming de novo resistance to immune checkpoint blockade, motivating the study of tumor microenvironment to overcome this resistance. Taking advantage of the vast public available prostate cancer genome database, I identified the chromatin remodeling protein CHD1 as a synthetic essential gene in PTEN-deficient PCa through regulating NF-KB pathway genes. **Method:** To investigate CHD1 function on prostate cancer progression, I generated PB-Cre, PtenL/L, Chd1L/L and PB-Cre, PtenL/L, Smad4L/L, Chd1L/L genetically engineered mouse (GEM) models, and performed histopathology analysis, transcriptomic profiling and immunophenotype profiling. **Results:** So far, delayed tumor development, decreased lymph node metastasis has been observed in Chd1 depleted prostate tissues. Importantly, a significantly prolonged overall survival has been observed in PtenChd1 DKO mice, compared to mice with Pten knockout PCa. To further uncover the mechanism underlying the CHD1 depletion phenotype, unbiased transcriptomic profiling was performed. In addition to several well-known oncogenic signaling pathways, such as EMT and Kras pathways, I also identified down-regulated inflammatory pathways upon CHD1 inhibition, prompting me to determine whether CHD1 affects TME remodeling in Pten-deficient PCa. Mass Cytometry (CyTOF) was also performed in PtenChd1 DKO mice to identify the immunophenotype, including CD4+ T-cells, CD8+ T-cells, regulatory T-cells (Tregs), B cells, dendritic cells, NK cells, granulocytic/monocytic myeloid-derived suppressor cell (MDSCs), and tumor-associate macrophages (TAMs). The data suggested that the levels of MDSCs, which play key roles in immune suppression, were significantly reduced in PtenChd1 DKO prostate tumors; correspondingly, CHD1 depletion boosted tumor-infiltrating CD8+ T-cells, rather than CD4+ T-cell, NK cells or B cells. Consistently, I observed that human PCa tumors with high CHD1 expression displayed significant enrichment of MDSCs gene signatures in TCGA database, and IHC staining in a human PCa tissue microarray also indicated a negative correlation between CHD1 and CD8+ T-cell infiltration. **Conclusions:** These data suggested that CHD1 plays essential roles on PTEN-deficient PCa, and CHD1 contributes to an immunosuppressive tumor microenvironment in PTEN-deficient PCa.

Conflict of Interest: None

Funding Acknowledgements: PCF Young Investigator Award; MD Anderson Odyssey Fellowship